Amendments to the Specification:

On page 1, please replace the paragraph entitled "Related Applications" with the following replacement paragraph.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of USSN 08/348,471, filed November 30, 1994 (now US 6,420,169), which is a continuation of USSN 07/805,727 (filed December 6, 1991, now U.S. Patent No. 5,424,186); which is a continuation-in-part of USSN 07/492,462 (filed March 7, 1990, now U.S. Patent No. 5,143,854); which is a continuation-in-part of USSN 07/362,901 (filed June 7, 1989, now abandoned). USSN 07/805,727 (filed December 6, 1991, now U.S. Patent No. 5,424,186) is also a continuation-in-part of USSN 07/624,120 (filed December 6, 1990, now abandoned); which is a continuation-in-part of USSN 07/492,462 (filed March 3, 1990, now U.S. Patent No. 5,143,854) and USSN 07/362,901 (filed June 7, 1989, now abandoned).

Please replace the paragraph beginning on page 8, line 2 entitled "BRIEF DESCRIPTION OF THE DRAWINGS" with the following amended paragraph:

FIGS. 1 to 7 illustrate masking, irradiation, and coupling of monomers;

FIGS. 8A and 8B are fluorescence curves for NVOC slides not exposed and exposed to light respectively;

FIGS. 9A-9D are fluorescence plots of slides exposed through 100 μm, 50 μm, 20 μm and 10 μm masks;

FIG. 10 illustrates fluorescence of a slide with the peptide YGGFL (SEQ. ID NO:1) on selected region on its surface which has been exposed to labeled Herz antibodies specific for the sequence;

[redacted]

FIG. 11 schematically illustrates one example of light-directed peptide synthesis;

FIG. 12 is a fluorescence plot of YGGFL (SEQ. ID NO:1) and PGGFL synthesized in a 50 .mu.m checkerboard pattern;

FIGS. 13A-13D illustrate formation and screening of a checkerboard pattern of YGGFL (SEQ. ID NO:1) and GGFL (SEQ. ID NO:15);

FIG. 14 is a fluorescence plot of YPGGFL (SEQ. ID NO:3) and YGGFL (SEQ. ID NO:1) synthesized in a 50 μm checkerboard pattern;

FIGS. 15A and 15B illustrate the mapping ~~maping~~ of 16 sequences synthesized on two different glass slides;

FIG. 16 is a fluorescence plot of the slide illustrated in FIG. 15A;

FIG. 17 is a fluorescence plot of the slide illustrated in FIG. 15B;

FIG. 18 is a fluorescence plot of an experiment which produced 4,096 compounds;

FIG. 19 is a fluorescence plot of a substrate on which 65,536 different compounds were formed;

FIGS. 20A and 20B show a tripeptide used in a fluorescence energy-transfer substrate assay and that substrate after cleavage;

FIGS. 21A and 21B are fluorescence plots generated with fluorescence energy-transfer substrate assays;

FIGS. 22A and 22B illustrate alterative embodiments of a reactor system for forming a plurality of polymers on a substrate;

FIG. 23 schematically illustrates an automated system for synthesizing diverse polymer sequences;

FIGS. 24A and 24B illustrate operation of a program for polymer synthesis;

FIG. 25 is a schematic illustration of a "pure" binary masking strategy;

FIG. 26 is a schematic illustration of a gray code binary masking strategy;

FIG. 27 is a schematic illustration of a modified gray-code binary masking strategy;

FIG. 28A schematically illustrates a masking strategy for a four step synthesis;

FIG. 28B schematically illustrates synthesis of 400 peptide dimers of genetically coded amino acids;

FIG. 29 is a coordinate map for the ten-step binary synthesis;

FIG. 30 is a fluorescence plot of a 4.times.10 array of peptides having sequences similar to dynorphin B;

FIG. 31 illustrates a strategy for producing an array of peptides related to the dynorphin B sequence;

FIG. 32 is a fluorescence plot of an array of peptides produced according to the strategy illustrated in FIG. 31;

FIG. 33 is a fluorescence plot of an array of peptides containing various deletions from the dynorphin B sequence;

FIG. 34 is a plot of the relative binding affinities of an anti-dynorphin B monoclonal antibody to various sequences produced on the substrate shown in FIG. 33;

FIG. 35 schematically illustrates a data collection system;

FIG. 36 is a block diagram illustrating the architecture of the data collection system;

FIG. 37 is a flow chart illustrating operation of software for the data collection/analysis system;

FIG. 38 schematically illustrates one example of light-directed oligonucleotide synthesis;

FIGS. 39A-39C are fluorescence plots demonstrating hybridization, dehybridization and rehybridization between immobilized poly A and poly T;

FIGS. 40A-40E illustrate a synthesis strategy for forming polysaccharides in accordance with the present invention; and

[redacted]

FIG. 41 illustrates the introduction of a reduced ~~1reduced~~ amide bond into a growing peptide.

Please replace the paragraph beginning on page 24, line 23 with the following amended paragraph:

According to other embodiments, a set of masks is used for the first monomer layer and, thereafter, varied light wavelengths are used for selective deprotection. For example, in the process discussed above, first regions are first exposed through a mask and reacted with a first monomer having a first protecting group P_1, which is removable upon exposure to a first wavelength of light (e.g., IR). Second regions are masked and reacted with a second monomer having a second protective ~~protecive~~ group P_2 which is removable upon exposure to a second wavelength of light (e.g. UV). Thereafter, masks become unnecessary in the synthesis because the entire substrate may be exposed alternatively to the first and second wavelengths of light in the deprotection cycle.

Please replace the paragraph beginning on page 29, line 19 with the following amended paragraph:

The surface 10 of the substrate is preferably provided with a layer of linker molecules 12, although it will be understood that the linker molecules are not required elements of the invention. The linker molecules are preferably of sufficient length to permit polymers in a completed substrate to interact freely with molecules exposed to the substrate. The linker molecules should be 6-50 atoms long to provide sufficient exposure. The linker molecules may be, for example, aryl acetylene, ethylene glycol oligomers containing 2-10 monomer units, diamines, diacids, amino acids, or combinations thereof. Other linker molecules may be used in light of this disclosure ~~disclsoure~~.

Please replace the paragraph beginning on page 34, line 27 with the following amended paragraph:

While the invention is illustrated primarily herein by way of the use of a mask to illuminate selected regions of the substrate, other techniques may also be used. For example, the substrate may be translated under a modulated laser or diode light source. Such techniques are discussed in, for example, U.S. Pat. No. 4,719,615 (Feyrer et al.), which is incorporated herein by reference. In alternative embodiments a laser galvanometric scanner is utilized. In other embodiments, the synthesis may take place on or in contact with a conventional liquid crystal (referred to herein as a "light valve") or fiber optic light sources. By appropriately modulating liquid crystals, light may be selectively controlled so as to permit light to contact selected regions of the substrate. Alternatively, synthesis may take place on the end of a series of optical fibers to which light is selectively applied. Other means of controlling the location of light exposure will be apparent to those of skill in the art.

Please replace the paragraph beginning on page 42, line 1 with the following amended paragraph:

FIG. 8A illustrates the slide which was not exposed to light, but which was exposed to FITC. Fluorescence on the surface was measured by excitation using 488 nm laser light and photomultiplier detection through appropriate fluorescein ~~fluuorescein~~ emission filters described in additional detail below. The units of the x axis are time (msec) and the units of the y axis are counts. The trace contains a certain amount of background fluorescence. The duplicate slide was exposed to 350 nm broadband illumination for about 1 minute (12 mW/cm.sup.2, -350 nm illumination), washed and reacted with FITC. The fluorescence curves for this slide are shown in FIG. 8B. A large increase in the level of fluorescence is observed, which indicates photolysis has exposed a number of amino groups on the surface of the slides for attachment of a fluorescent marker.

Please replace the paragraph beginning on page 55, line 15 with the following amended paragraph:

Next a process file was generated on the program "PS" (copy provided in Appendix 3). This was done by hitting F1 (if an IBM computer was being used to run the

program) to "initialize masking sequence." "Binary process minimum movement" was chosen and then the program asked for input of the building blocks in order of C terminus to N terminus. The first building block that was input that goes onto the chip first, in this case S. The program allows for input of the names in either one letter or three letter codes. Using a binary process with minimum movement, one does not have to select the mask that will be used, as the program will select the mask. For a sixteen-step binary synthesis the following masks are used in the order given: mask A offset 0, mask A offset 1, mask B offset 0, mask B offset 1, mask C offset 0, mask C offset 1, mask D offset 0, mask D offset 1, mask E offset 0, mask E offset 1, mask F offset 0, mask F offset 1, mask G offset 0, mask G offset 1, mask H offset 0, and mask H offset 1. The masking sequence was then saved to disk so that it could be used during data workup.

Please replace the paragraph beginning on page 84, line 26 with the following amended paragraph:

It is often desirable to deduce a binding affinity of a given peptide from the measured fluorescence intensity. Conceptually, the simplest case is one in which a single peptide binds to a univalent antibody molecule. The fluorescence scan is carried out after the slide is washed with buffer for a defined time. The order of fluorescence intensities is then a measure primarily of the relative dissociation rates of the antibody-peptide complexes. If the on-rate constants are the same (e.g., if they are diffusion-controlled), the order of fluorescence intensities will typically correspond to the order of binding affinities. However, the situation is sometimes more complex because a bivalent primary antibody and a bivalent secondary antibody are used. The density of peptides in a synthesis area corresponded to a mean separation of .about.7 nm, which would allow multivalent antibody-peptide interactions. Hence, fluorescence intensities obtained according to the method herein will often be a qualitative indicator of binding affinity. For a more complete analysis of how the present invention can be extended to the binding affinity of an immobilized ligand to a receptor, see U.S. Ser. No. 07/796,947, filed Nov. 22, 1991, now U.S. Pat. No. 5,324,633 and incorporated herein by reference.

Please replace the paragraph beginning on page 90, line 27 with the following amended paragraph:

Four classes of peptide were produced: (1) RYKVVT (SEQ. ID NO:32), (2) RQYKVVT (SEQ. ID NO:33), (3) RQYFKVVT (SEQ. ID NO:34), and (4) RYFKVVT (SEQ. ID NO:35). In each case Y represents all 20 L-amino acids. FIG. 32 is an image of a fluorescence scan prepared after the final array of peptides was exposed to anti-dynorphin B mouse monoclonal ~~monocolonal~~ antibody followed by goat anti-mouse antibody. The top one-fourth of the image was prepared according to the synthesis procedure outlined above.

Please replace the paragraph beginning on page 132, line 16 with the following amended paragraph:

Two other synthetic routes (shown below) which may be employed to synthesize β-amino acids take advantage of the functional relation of β-lactams (which have well-known chemistries) and .beta.-amino acids. These methods are detailed in various references, including Kamal et al., Heterocycles (1987) 26:1051-1076 and Hart et al., Chem. Rev. (1989) 89,:1447-1465, both of which are incorporated herein by reference for all purposes. The first synthetic route exploits the cycloaddition reactions of chlorosulfonyl isocyanate (CSI) with alkenes to give, after hydrolysis, β-lactams. These can then be hydrolyzed to give the corresponding ~~the~~ β-amino acids. Because of the polar mechanism for the CSI cycloaddition, it is not possible to use this reaction to prepare type III compounds which have no substitution on the carbon atom adjacent to the nitrogen atom. The second route employs the condensation of enolates with imines, to produce β-lactams. Optically active compounds are provided by this method, but the basic reaction with diazomethane gives only type IV structures. Type II structures may be prepared if diazomethane is substituted with diazoethane and the resulting diastereomers are separated. This synthesis route has the added advantage that it may directly provide protected amino acids for peptide synthesis.

Please replace the paragraph beginning on page 138, line 1 with the following amended paragraph:

One advantage of this homologous series of compounds is that a unified synthetic approach can be employed. For example, the cycloaddition of chlorosulfonylisocyanate with cycloalkenes may be utilized. This is most applicable to cis isomers of cyclopentyl and cyclohexyl systems. Enantiomer selective enzymatic hydrolysis of the β-lactam then gives the desired β-amino acids ready for derivatization. A second route is more general, and longer. It begins with 1,2-cycloalkanedicarboxylic esters (or their derived diol acetates), which can be prepared via Diels-Alder reactions of maleates or from dianion alkylation of succinate as described ~~decribed~~ in Garratt et al., Tetrahedron Lett. (1987) 28:351-352 which is incorporated herein by reference for all purposes. Enzymatic transformation then introduces optical activity and differentiates the carboxyl groups, which permits selective conversion of one into an amino group as described in Sabbioni et al., J. Org. Chem. (1987) 52:4565-4570 which is incorporated by reference herein for all purposes. One advantage of this strategy ~~stategy~~ is that it directly provides the amino protected building block.